BENAROYA RESEARCH INSTITUTE
Virginia Mason

Protocol

Modulation of STAT3 Signaling with Siltuximab in Type 1 Diabetes

EMU-002

Short Title: STAT3 Modulation with Siltuximab

Version 1.1

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1 ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BRI	Benaroya Research Institute at Virginia Mason
CBC	Complete blood count
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
CRF	Case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DKA	Diabetic ketoacidosis
EBV	Epstein-Barr virus
FDA	US Food and Drug Administration
GAD-65	Glutamate decarboxylase-65
GCP	Good clinical practice
HbA1c	Glycosylated hemoglobin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
IA-2	Insulinoma antigen-2
IMDRR	Immune-Mediated Disease Registry and Repository
ICH	International Conference on Harmonization
IL-17	Interleukin-17
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
IRB	Institutional review board
LDL	Low-density lipoprotein
LFT	Liver function test
MCD	Multicentric Castleman's disease
MMTT	Mixed-meal tolerance test
PBMC	Peripheral blood mononuclear cell
PPD	Purified protein derivative
p-STAT3	Phosphorylated signal transducer and activator of transcription 3
RA	Rheumatoid arthritis
SAE	Serious adverse event
STAT3	Signal transducer and activator of transcription 3
T1D	Type 1 diabetes
Teff	Effector T cells
Treg	Regulatory T cells
TB	Tuberculosis
ULN	Upper limit of normal range
VMMC	Virginia Mason Medical Center
ZnT8	Zinc transporter-8

2. PROTOCOL SYNOPSIS

Title	Modulation of STAT3 Signaling with Siltuximab in Type 1 Diabetes
Protocol Number	EMU-002
Short Title	STAT3 Modulation with Siltuximab
Sponsor Investigator	Carla Greenbaum, MD
Conducted at	Benaroya Research Institute at Virginia Mason Clinical Research Center 1201 Ninth Ave Seattle, WA 98101
Funding Organization	Janssen Research &Development, LLC.
Accrual Objective	10 subjects
Test Product and Route of Administration	Commercially sourced Siltuximab (100 mg lyophilized powder in single-use vial for intravenous infusion)(SYLVANT™)
Study Design	This trial is a single arm, open-label, single-dose, mechanistic endpoint clinical study of Siltuximab in adult subjects diagnosed with type 1 diabetes (T1D). Eligible subjects will receive a single intravenous infusion of 11 mg/kg Siltuximab with blood samples for primary outcome obtained 12 weeks later.
Primary Objective	To determine whether Siltuximab can durably suppress the p-STAT3 response to IL-6.
Primary Endpoints	Change in IL-6 stimulated intracellular p-STAT3 between Week 12 and baseline
Secondary Endpoints	• Change in IL-6 stimulated intracellular pSTAT-3 between Week 2 (post-treatment) and baseline. • Change in IL-6 stimulated intracellular p-STAT3 between Week 2 (post-treatment) and Week 12. • Sensitivity of effector T cells to suppression by regulatory T cells • Frequency of effector T cells secreting IL-17 and other cytokines • Correlation of circulating levels of Siltuximab to the p-STAT3 response
Safety Endpoints	•Adverse events associated with Siltuximab treatment
Major InclusionCriteria	•M/F 18-45 years of age, inclusive •Diagnosis of T1D within 10 years of enrollment

3. BACKGROUND AND RATIONALE

Type 1 diabetes (T1D) affects around 1 million people in North America, with an incidence of approximately 30,000 new pediatric and adult cases per year. The current standard of care does not eliminate the risk of acute life-threatening hypoglycemic and hyperglycemic events [1], and patients with T1D are at high risk for long-term complications.

A goal of disease modifying therapy in T1D is to halt the autoimmune process, ideally prior to the onset of clinical symptoms, in order to preserve the maximum level of beta cell function. Even if endogenous insulin production capacity is severely compromised, there is still a benefit of maintaining even low levels of residual beta cell function [2], [3]. Phase 2 trials of Abatacept [4], Rituximab [5], Teplizumab [6], and Alefacept [7] have demonstrated that therapies directed against T cells and B cells can delay further loss of beta cell function, directly implicating a role for adaptive immunity in the pathogenesis of the disease. While promising, clinical adoption of immune-based therapies will likely require therapies demonstrating more pronounced efficacy for longer durations of time. In order to develop more targeted and effective immunotherapies in T1D, there is a need to identify immune pathways that are dysregulated in affected patients and to test specific interventions in those pathways.

3.1. Rationale for Study

One potential target for further investigation in T1D is the IL-6 pathway. IL-6 is an innate immune cytokine that is central to activation of the adaptive immune system by regulating the balance between suppression and activation of effector responses. Exposure to IL-6 during T cell activation promotes the differentiation of Th17 cells that produce highly pro-inflammatory cytokines such as IL-17. Th17 cells are elevated in patients with T1D [8], [9] and IL-17 has been shown to have direct cytotoxic effects on beta cells [10]. Conversely, whereas regulatory T cells (Tregs) dominantly suppress the activity of effector T cells under homeostasis, innate immune activation releases effector T cells from Treg suppression, a process that can be mediated by IL-6[11]. This state of T effector resistance has been observed in both T1D [12] and in other autoimmune diseases such as multiple sclerosis. In the latter, effector cell sensitivity to regulation could be restored by blocking IL-6 signaling [13]. Consistent with these findings, treatment with the IL-6R blocking antibody Tocilizumab reduces the frequency of Th17 cells and increases the frequency of Tregs in patients with rheumatoid arthritis (RA) [14].

Notably, a subset of patients with T1D display a pattern of abnormally strong responses to IL-6, as measured by phosphorylation of the transcription factor STAT3 (Buckner and colleagues, unpublished). We hypothesize that elevated responsiveness to IL-6 may be due to elevated IL-6 activity in vivo and that patients with this phenotype may be especially responsive to intervention in this pathway. We have previously demonstrated a long term impact of biologic therapies on the IL-2 signaling pathway using cytokine receptor signaling as measured by p-STAT5 as a functional readout [15]. In this study, we will test whether we can observe a similar modulation of

signaling in another cytokine pathway implicated in T1D, the IL-6-dependent p-STAT3 pathway, using Siltuximab (SYLVANT™). Siltuximab, developed by Janssen Research and Development, LLC; is an anti-IL-6 antibody approved in the US for the treatment of multicentric Castleman's disease (MCD). We will test whether temporary blockade of the IL-6/IL-6R pathway will decrease the sensitivity of PBMCs to IL-6 *ex vivo*, using the IL-6-dependent phosphorylation of STAT3 as the primary endpoint. In addition, we will investigate whether changes in IL-6 signaling are associated with other immune effects, such as reduction in effector T cell responses or increases in the sensitivity of effector T cells to suppression.

4. STUDY OBJECTIVES

4.1. Primary Objective

Determine whether Siltuximab can durably suppress the phospho-STAT3 (p-STAT3) response to IL-6. Durable response is defined as a suppressed p-STAT3 response 12 weeks post-infusion of Siltuximab.

4.2. Secondary Objectives

- Assess the pharmacodynamic effects of Siltuximab on IL-6-dependent p-STAT3 signaling at different time points post-treatment
- Determine if Siltuximab can increase the sensitivity of effector T cells to suppression by regulatory T cells
- Determine if Siltuximab can decrease the frequency of T cells secreting IL-17 or other effector cytokines
- Correlate of circulating levels of Siltuximab to the p-STAT3 response

4.3. Exploratory Objectives

Other mechanistic studies as appropriate.

4.4. Safety Objective

Evaluate adverse effects associated with single-dose infusion of Siltuximab in subjects with T1D.

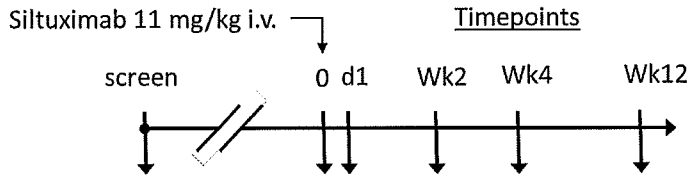
5. STUDY DESIGN

5.1. Overview

This trial will be conducted as a single arm, open-label, single-dose, mechanistic endpoint study of Siltuximab in adult subjects diagnosed with type 1 diabetes (T1D). Subjects diagnosed with T1D and meeting eligibility criteria will receive a single intravenous infusions of 11 mg/kg

Siltuximab. An abbreviated Schedule of Events is provided in Figure 1 to illustrate the study design.

Figure 1. Overview of study assessments.



MMTT	X					
Clinical Laboratory Assessments	X	X	X	X	X	
Primary Endpoint: IL-6 p-STAT3	X	X	X	X	X	
Additional Mechanistic Assays	X	X	X	X	X	

6. CRITERIA FOR EVALUATION

6.1. Primary Endpoint

- Change in IL-6 stimulated intracellular p-STAT3 between Week 12 and baseline.

6.2. Secondary Endpoints

- Change in IL-6 stimulated intracellular p-STAT3 between Week 2 and Baseline.
- Change in IL-6 stimulated intracellular p-STAT3 between Week 2 and Week 12.
- Sensitivity of effector T cells to suppression by regulatory T cells
- Frequency of effector T cells secreting IL-17 and other cytokines
- Correlation of circulating Siltuximab concentration to p-STAT3 response

7. SUBJECT SELECTION

7.1. Study Population

Study subjects will include males and females 18-45 years of age with a diagnosis of Type 1 diabetes within 10 years of enrollment.

7.2. Inclusion criteria

Each potential subject must satisfy all of the following criteria before enrollment:

1. Positive for at least one diabetes-related autoantibody any time since diagnosis, including by not limited to:

- Glutamate decarboxylase (GAD-65) Insulin, if obtained within 10 days of the onset of exogenous insulin therapy
- IA-2
- ZnT8

2. Peak stimulated C-peptide level ≥ 0.1 pmol/mL following a mixed meal tolerance test (MMTT) conducted within 60 days of enrollment
3. Females of child-bearing potential must be willing to use effective birth control and refrain from donating eggs for the purposes of assisted reproduction for duration of study.
4. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening and prior to dosing.
5. During the study, and for 3 months after receiving the study agent, a woman must agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction.
6. Willing and able to give informed consent for participation.

7.3.Exclusion criteria

Any potential subject who meets any of the following criteria before enrollment will be excluded from participating in the study.

1. History of severe reaction or anaphylaxis to human, humanized or murine monoclonal antibodies;
2. History of malignancy or serious uncontrolled cardiovascular disease or hypertension, nervous system, pulmonary, renal, or gastrointestinal disease, or significant dyslipidemia despite therapy;
3. Any history of recent (within 3 months) serious bacterial, viral, fungal, or other opportunistic infections;
4. History or serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C;
5. Positive QuantiFERON or PPD TB test, history of tuberculosis, or active TB infection;
6. Active infection with EBV as defined by EBV viral load ≥ 10,000 copies per mL of whole blood;
7. Active infection with CMV as defined by CMV viral load ≥ 10,000 copies per mL of whole blood;
8. Diagnosis of liver disease or elevated hepatic enzymes, confirmed by repeat tests, as defined by ALT, AST, or both > 1.5 x the upper limit of age-determined normal (ULN) or total bilirubin > ULN;

9. Any of the following hematologic abnormalities, confirmed by repeat tests:
   - White blood count <3,000/μL or >14,000/μL
   - Lymphocyte count <500/μL
   - Platelet count <150,000 /μL
   - Hemoglobin <8.5 g/dL or ≥ 17 g/dL
   - Neutrophil count <2,000 cells/μL
10. Females who are pregnant or lactating;
11. Receipt of live vaccine (e.g. varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, bacillus Calmette-Guérin, and small pox) in the 6 weeks before treatment;
12. Receipt of non-live vaccine in the 4 weeks before treatment;
13. Any medical or psychological condition that in the opinion of the Sponsor Investigator would interfere with the safe completion of the trial;
14. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 3 months or 5 half-lives before enrollment or is currently enrolled in the treatment stage of an investigational study;
15. Received any immune-modulating biologic drug within 3 months of enrolling in the study.

8. CONCURRENT MEDICATIONS

8.1. Vaccinations

Subjects must not be administered live vaccines (e.g. varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, bacillus Calmette-Guérin, and small pox) in the 6 weeks before treatment and 30 days post administration because of potential adverse outcomes of receiving live vaccination when immunosuppressed.

While not a safety concern, subjects should also not be administered any vaccines in the four weeks before and 12 weeks post treatment as vaccination may influence the study outcome.

8.2. Potential Drug Interactions

No *in vitro* or *in vivo* drug-drug interaction studies have been conducted with Siltuximab, however cytochrome P450s in the liver are down regulated by infection and inflammation stimuli including IL-6. Therefore Siltuximab may affect the way some medicines work over time (e.g., atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine, benzodiazepines, and oral contraceptives. Given the short duration of

exposure to Siltuximab in this study (single dose), it is unlikely that any dose adjustment of these drugs is warranted.

9. STUDY TREATMENT

Siltuximab (SYLVANT™) is an interleukin-6 (IL-6) monoclonal antibody antagonist indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative. Siltuximab has not be studied in patients with Type 1 diabetes.

9.1.Test Formulation

Siltuximab is provided in single-use vials containing 100 or 400 mg of lyophilized powder. The product is administered as an 11 mg/kg dose given over approximately 1 hour by intravenous infusion.

Instructions for preparation and administration of the drug is reviewed in Section 10.4. Complete dosing instructions are provided in the SYLVANT prescribing information (Attachment 2).

9.2.Supply of Study Medication

Commercially-sourced SYLVANT® Product will be provided by Janssen Research & Development, LLC for this study. The product will be stored by the VMMC Investigational Pharmacy and formulated on the day of infusion.

9.3.Study Medication Accountability

Individual doses of formulated Siltuximab will be prepared for intravenous administration by VMMC Investigational Drug Services. A drug administration log will be kept current for each participant and will contain the identification of each participant and the date and quantity of drug dispensed. All remaining unused investigational product will be destroyed locally.

9.4.Dosing

Siltuximab will be administered at a dose of 11 mg/kg as a single intravenous infusion. Dosing will be according to the individual's weight during the screening visit and the value will be rounded up by excess to the next half kilogram; i.e. 45.6 kg weight will be rounded up to 46 kg.

The Siltuximab lyophilized powder will be reconstituted according to the manufacturer's instructions (SYLVANT PACKAGE INSERT). Briefly, Siltuximab will be dissolved under aseptic conditions to a concentration of 20 mg/mL Dextrose 5% in Water. The lyophilized powder should dissolve in less than

60 minutes. Once reconstituted, and prior to further dilution, the vials must be inspected for

particulates and discoloration. Vials containing particulates or solution discoloration are discarded. The constituted product can be kept for no more than two hours prior to addition into an infusion bag. The reconstituted product is subsequently added to a 250 mL infusion bag containing 250 mL sterile Dextrose 5% in Water.

Siltuximab will be administered intravenously over approximately 60 minutes. Subjects will be observed in the clinic for approximately 15 minutes after the end of the infusion. Vital signs (blood pressure and pulse) will be recorded within 10 minutes before, 15 minutes during, at the end, and within approximately 15 minutes after completion of the infusion. The infusion should be completed within 4 hours of the dilution of the reconstituted solution to the infusion bag.

10.STUDY PROCEDURES AND GUIDELINES

10.1.Clinical Assessments

A schedule of procedures is provided in Attachment 1. Descriptions of all assessments are described in subsequent sections.

10.1.1.General Assessments

- Informed consent: written informed consent will be obtained from the participant before any study assessments or procedures are performed;
- Eligibility criteria: eligibility for study participation will be assessed during the screening period;
- Medical History: Relevant medical history, including history of current and previous disease, and review of systems will be obtained. Adverse events will be assessed. A directed physical exam will be conducted as indicated by medical history;
- Concomitant medications: concomitant medications and their indications will be recorded;
- Vital Signs: Body temperature, blood pressure, pulse and respirations will be measured at Screening (Visit 1) and Baseline (Visit 2).

10.1.2.Clinical Laboratory Assessments

- Islet autoantibodies. Antibody levels will be measured for all subjects at screening. Previously recorded evidence of one or more islet antibodies may be used to satisfy eligibility;
- Serum chemistries: Electrolytes (sodium, potassium, chloride, phosphate, total CO2), blood urea nitrogen (BUN), creatinine, CRP and liver panel (AST, ALT, alkaline phosphate, direct and total bilirubin);
- Hematology: Includes RBC, hematocrit, hemoglobin, platelet count, WBC and differential, and erythrocyte sedimentation rate;

- Lipid panel: Total cholesterol, HDL, LDL, triglycerides;
- Infectious disease serology: Serology will be performed at screening for HBV, HCV, HIV, EBV, CMV;
- Viral load testing: Viral load testing by PCR will be performed for CMV and EBV at screening;
- QuantiFERON TB test or PpD: Exposure to tuberculosis will be assessed via QuantiFERON TB test or PPD;
- Pregnancy testing: Females with reproductive capacity will undergo urine pregnancy testing at screening and prior to drug administration.

10.1.3. Metabolic Assessments

- 2-hour mixed meal tolerance test;
- HbA1c;
- Insulin use and home blood glucose measurements.

10.2. Pharmacokinetic Assessments

10.2.1. Correlation of Drug Concentration to p-STAT3 Response

The primary objective of this study is to determine whether Siltuximab can durably suppress the p-STAT3 response to IL-6. A durable response is defined as a suppressed p-STAT3 response, compared to baseline; that persists up to 12 weeks post-infusion. In order to analyze the correlation between serum concentrations of Siltuximab and p-STAT3 suppression, blood will be obtained at each visit for measurement of the Siltuximab concentration (see Attachment 1, Schedule of Events). The serum concentration data will be used in a cross-correlation analysis with p-STAT3 levels assessed at the same time points.

10.3. Mechanistic Assessments

10.3.1. IL-6 Induced p-STAT3

The primary objective of this study is to determine whether Siltuximab can durably suppress the phospho-STAT3 (p-STAT3) response to IL-6. The methods used to assess p-STAT3 may change as new assay become available, but are currently expected to be as follows. PBMC will be incubated with recombinant human IL-6 and then analyzed by flow cytometry after intracellular staining with a p-STAT3-specific antibody. The degree of STAT3 phosphorylation will be determined both before and after IL-6 stimulation. The change in phosphorylation levels will be quantified for each sample and will be compared before and after Siltuximab exposure. As the primary endpoint, we will determine whether the induction of p-STAT3 by IL-6 is significantly reduced at Week 12 compared to baseline.

10.3.2.Additional Mechanistic Assays

This study also aims to correlate changes in p-STAT3 signaling with changes in other immune and genetic parameters such as, but not limited to, those listed below.

10.3.2.1.T Cell Cytokine Assay.

To assess the function of effector T cells, PBMC from study subjects and healthy controls, may be stimulated with mitogens or other appropriate stimuli in the presence of Golgi inhibitors, followed by intracellular staining for IL-17, IFN-γ, and/or other cytokines and functional markers. We may determine whether the frequency of cytokine positive T cells is significantly different after Siltuximab exposure compared to baseline.

10.3.2.2.Suppression Assay.

We may test the hypothesis that effector T cell sensitivity to suppression will be increased after Siltuximab treatment. In this assay, Teff cells from study subjects and healthy controls are stimulated in the presence or absence of Treg isolated from healthy controls at a range of Treg: Teff ratios, and the degree of suppression after drug exposure is compared to baseline.

10.3.2.3.Other assays

We will perform additional exploratory analyses to determine what factors correlate with the degree of p-STAT3 modulation by Siltuximab. These factors may include age, duration of disease, HLA type, single nucleotide polymorphisms, measures of glycemic control such as HbA1c, and baseline p-STAT3 responses in study subjects and healthy controls.

Specific assays required to complete these analyses include other immune and genetic assays such as:

- Whole blood and cellular transcriptomics, histocompatibility antigen typing, single nucleotide polymorphism (SNP) analysis, genotyping, signaling responses to cytokines in addition to IL-6, antigen specific T-cell assays (CD4 and CD8), serum cytokines, serum proteomics, and miRNAs;
- Samples will be stored for these supplemental assays.

11.ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1.Overview

As the sponsor of the Study, the Sponsor Investigator shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating co- or sub-investigators, as defined in applicable laws and

regulations.

11.2.Definitions

11.2.1.Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

11.2.2.Unexpected or Unlisted Adverse Event

An adverse event is considered unexpected or unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information (http://www.sylvant.com/shared/product/sylvant/sylvant-prescribing-information.pdf).

11.2.3.Adverse Events of Special Interest

Adverse events of Special Interest include events that Janssen Research & Development is actively monitoring as a result of previously identified signals detailed in the SYLVANT prescribing information. These adverse events are:

- Infections
- Hepatotoxicity
- Gastrointestinal Perforations
- Hemoglobin increases, including polycythemia

11.2.4.Serious Adverse Event (SAE)

A serious adverse event (SAE) or reaction is defined as "any adverse event occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution." An adverse event or suspected adverse reaction is considered "serious" if, in the view of the sponsor investigator, it results in any of the following outcomes:

- Death. A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy must be reported whether it is considered to be treatment related or not;
- A life-threatening adverse event. A life-threatening event is any adverse therapy experience that, in the view of the investigator, places the participant at immediate risk of death from the reaction as it occurred;
- Inpatient hospitalization or prolongation of existing hospitalization with the exception of hospitalization relating to glycemic control in type 1 diabetes;
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Congenital anomaly or birth defect;
- Important medical events* that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above;
- Is a suspected transmission of any infectious agent via a medicinal product

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

11.2.5.Special Reporting Situations

Adverse events of interest for a Janssen medicinal product that require expedited reporting and/or safety valuation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal);
- Overdose of a Janssen medicinal product;
- Exposure to a Janssen medicinal product from breastfeeding;
- Suspected abuse/misuse of a Janssen medicinal product;
- Inadvertent or accidental exposure to a Janssen medicinal product;
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion);
- Suspected transmission of any infectious agent via administration of a medicinal product;
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Research & Development perspective, they are treated in the same manner as adverse events.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY within 24 hours of becoming aware of the event.

11.2.6.Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., auto injector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

11.3.Safety assessments and Collection of Safety Data

This is an exploratory study designed to assess the effects of a single dose of Siltuximab on a select set of immune parameters. All adverse events, regardless of causality, special reporting situations, and product quality complaints will be collected from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety).

The Investigator(s) will treat participants with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize. Adverse events may be discovered through:

- observation of the participant;
- questioning the participant;
- unsolicited complaints by the participant.

All serious adverse events, adverse events of special interest, product quality complaints, and special situations including pregnancies, whether serious or non-serious, related or not related, following exposure to Siltuximab will be documented by the Sponsor Investigator (or sub-Investigators) and recorded in subject's source documents. Events will be assessed and reported consistent with the ICH Guideline for Good Clinical Practice, 21 CFR 312.32 for expedited safety reporting, per the guidance of the DHHS Office for Human Research Protections (OHRP), and according to any reporting requirements outlined in this protocol.

Adverse events with the exception of hypoglycemia or hyperglycemia will be graded per the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.03 (published May 28, 2009). An adverse hypoglycemic event is defined as one resulting in loss of consciousness, seizure, or requiring assistance of others due to altered state of consciousness. An adverse hyperglycemic event is one resulting in diabetic ketoacidosis (DKA).

Duration (start and stop dates and times), severity/grade, outcome, treatment and relationship to study drug (not, unlikely, possibly, probably, or definitely related) will be recorded on source documents. The batch and lot number of the product will be recorded for all patients, including dose and date of infusion.

11.3.1.SAEs and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves;
- The event stabilizes;
- The event returns to baseline, if a baseline value/status is available;
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct; or

It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts.

11.4.Procedures for Reporting to Janssen Research & Development

The Sponsor Investigator will provide safety information to Janssen Research & Development on adverse events, special situations including pregnancies and product quality complaints as defined within this section.

11.4.1.Serious Adverse Events

Serious adverse events that are unexpected and possibly or probably drug related as defined in Section 11.2.4 will be reported to Janssen Research & Development using FDA Form MedWatch 3500A within 24 hours of becoming aware of the event. Serious adverse events, with the exception of pregnancies, will be reported for 30 days after the last dose of study drug.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the Sponsor Investigator, within 24 hours of becoming aware, to Janssen Research & Development.

All available clinical information relevant to the evaluation of a related SAE or special situation is required. The Sponsor Investigator is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same time line as initial reports and contain the elements summarized in section 11.2.5.

11.4.2..Adverse Events of Special Interest

Adverse events of special interest (≥ Grade 2), as defined in Section 11.2.2, will be reported to Janssen Research & Development on a quarterly basis unless they are serious adverse events. Serious adverse events will be reported within 24 hours of learning of the event.

11.4.3.Pregnancies

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further participation.

Pregnancies in female participants or partners of male participants will be reported to Janssen Research and Development within 24 hours of learning of the event using the FDA MedWatch 3500 A form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. Depending on local legislation this may require prior consent of the partner of the male participant.

Any abnormal pregnancy outcomes (e.g., spontaneous abortions, fetal demise, stillbirths, and congenital anomalies) will be reported to Janssen as an adverse event. Safety information to be included in each safety report is summarized in section 11.2.5.

11.4.4.Special Reporting Situations

Special Reporting Situations that occur during the study period, as defined in Section 11.2.5, will be reported to Janssen Research & Development on a quarterly basis unless they are serious adverse events. Serious adverse events will be reported using the MedWatch 3500A Form within 24 hours of becoming aware of the event. Safety information to be included in each safety report is summarized in section 11.2.5.

11.4.5.Individual Case Safety Report (ICSR)

All reports of serious adverse events must contain the elements described for Individual Case Safety Reports (ICSR). A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)

11.4.6.Product Quality Complaints (PQC)

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Research & Development, and are mandated by regulatory agencies worldwide. Janssen Research & Development has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Research & Development by the Sponsor Investigator within 24 hours after being made aware of the event. The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the Sponsor Investigator must report the PQC to Janssen Research & Development according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Research & Development.

11.5.Maintenance of Safety Information

All safety data will be maintained on source documents.

12.STATISTICAL METHODS

12.1.Primary Endpoint

We will analyze the change in IL-6-induced p-STAT3 mean fluorescence intensity at each time point in the study. Based on the published pharmacodynamics of Siltuximab, a maximal reduction in p-STAT3 signaling is expected to occur two weeks post-infusion. The correlation of a p-STAT3 response to Siltuximab treatment will be assessed by comparing the mean p-STAT3 ΔMFI at Screening to Baseline () using a paired two-tailed t-test. This represents random biological variability of the measurement over time. We will also compare the mean p-STAT3 ΔMFI at baseline to that at 2 weeks following infusion. This comparison will determine if we can reject the null hypothesis that Siltuximab does not modulate IL-6-dependent p-STAT3.

To determine if Siltuximab induces a durable reduction in p-STAT3, defined as maintenance of a moderated response 12 weeks after infusion, we will compare the mean p-STAT3 ΔMFI at Week 12) to the mean p-STAT3 ΔMFI at Baseline, using a paired 2-tailed t-test.

We will perform additional exploratory analyses to determine what factors correlate with the degree of p-STAT3 modulation by Siltuximab. These factors may include age, duration of disease, HLA type, single nucleotide polymorphisms, measures of glycemic control such as HbA1c, circulating concentration of Siltuximab, and baseline p-STAT3 responses.

12.2.Sample Size Rationale

Based on previous studies, the mean IL-6 induced p-STAT3 ΔMFI in T1D patients is 3.2 with a standard deviation of 1.3. Assuming a similar standard deviation before and after treatment, an α of 0.05 and power (1-β) of 0.8, the number of subjects required to detect a 50% reduction in the mean p-STAT3 ΔMFI using a paired t-test is 9 subjects. We propose enrollment of 10 subjects with evaluable data in order to ensure at least this level of power.

13.DATA COLLECTION, MONITORING, AND SAMPLE RETENTION

13.1.Data Collection Instruments

The Sponsor Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug. Data from source documents will be entered into a clinical database. The Sponsor Investigator is responsible for all information collected on subjects enrolled in this study.

13.2.Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

13.3.Monitoring

This study will be monitored by representatives of the Benaroya Research Institute Clinical Research Program Administrative Office according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6).

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) will be available for monitors and maintained for at least two years after the study is completed.

13.4.Sample Retention

Specimens collected in this trial, including genetic samples, will be deposited into the BRI Immune-Mediated Diseases Registry and Repository (IMDRR) for future research studies that have not yet been planned. Samples will be coded and stored indefinitely at the Benaroya Research Institute (BRI) in the IMDRR. We may share coded samples with colleagues at other institutions, who are doing research related to diabetes and immune-mediated disease. Identifiable personal and clinical information or "Protected Health Information" (PHI) collected from subjects is entered into the Registry and linked to a coded number. Access to this link is limited by double password to individuals directly involved in the clinical research associated with the protocol. In general, no data containing PHI will be provided to recipient investigators from the IMDRR unless a Data Use Agreement (DUA) has been established and disclosure is approved by the IRB. Samples collected for pharmacokinetic analysis will be shipped frozen to the Janssen Research and Development Biologics Clinical Pharmacology laboratory.

14.ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

14.1.Benefit of Participation

This study will not provide any direct benefit to the study subjects aside from the general benefits of closer health monitoring associated with participating in a clinical study. Future patients may benefit from these studies by virtue of knowledge gained about the pathophysiology of blocking cell activation by IL-6.

14.2.Risks of Participation and Mitigation of Risks

The possible discomforts, side effects, and risks related to Siltuximab treatment are not all known. Most side effects are not serious. Some may be serious and may require treatment or additional testing. Side effects seen on research studies can result from a patient's disease, the experimental drug, other drugs, other diseases, or a combination of these. These side effects may or may not have been due to Siltuximab.

The risk of administering Siltuximab to T1D patients is considered low because (a) subjects will only

receive a single infusion of the drug, and (b) all subjects enrolled will have T1D, but no other medical conditions that increase their risk of adverse effects. Most of the reported adverse effects were associated with long-term administration of the drug. In patients receiving a single dose of drug, the primary risk is of a hypersensitivity reactions to the product. Approximately 750 individuals have been treated with Siltuximab. Of these, one patient experienced an anaphylactic reaction. Data from 249 patients treated with Siltuximab monotherapy form the basis of the safety evaluation of infusion-related reactions. Infusion related reactions were reported in 4.8% of these patients. Symptoms of infusion-related reactions consist of back pain, chest pain or discomfort, nausea and vomiting, erythema, and palpitations.

T1D patients enrolled in the EMU-002 study will be screened for previous reactions, including anaphylaxis to human, humanized or murine monoclonal antibodies. In addition, all infusions will occur on the Clinical Research Center where subjects are closely monitored by experienced personnel equipped with resuscitation medications to address any such reactions including anaphylaxis to study drug administration.

Other adverse effects reported in patients treated chronically with Siltuximab included upper respiratory infections, renal injury, lipidemia, and low platelet and neutrophil counts. These potential effects will be mitigated by excluding subjects with those pre-existing conditions from participation in the study.

Finally, the effect of Siltuximab on human sperm, pregnant women, breastfeeding women, unborn babies, or nursing infants has not been studied. For this reason female subjects enrolled in this study must have a pregnancy test to confirm that they are not pregnant. A full summary of reported adverse events is provided in the Prescribing Information.

14.3.Statement of Compliance

This study will be conducted in compliance with the protocol and consistent with current Good Clinical Practices (GCP), adopting the principles of the Declaration of Helsinki, and all applicable regulatory requirements (ICH E6, 45CFR46, and FDA 21CFR sections 11, 50, 56, 312).

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the Benaroya Research Institute at Virginia Mason Institutional Review Board (IRB). Any amendments to the protocol or consent materials will also be approved by the IRB.

14.4.Informed Consent

The process of assuring that individuals (and parent/guardian if less than 18 years of age) are making an informed decision about participating in this study includes both verbal and written communication. All participants must read, sign, and date a consent form before participating in the study, taking the study drug, and/or undergoing any study-specific procedures.

The informed consent form must be updated or revised whenever important new safety

information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the informed consent will be given to a prospective participant for review. The attending health care provider will review the consent and answer questions.

14.5.Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the Investigator feels that it is not in the subject's best interest to continue. All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the Sponsor Investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

Individuals without evaluable mechanistic data may be replaced.

14.6.Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number. This number, rather than the participant's name, will be used in data analysis and reports.

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16.ATTACHMENTS

Attachment 1. Schedule of Procedures

Attachment 2. SYLVANT Prescribing Information and Dosing Instructions
(http://www.sylvant.com/shared/product/sylvant/sylvant-prescribing-information.pdf)

ATTACHMENT 1. Schedule of Events

Table 1. Study Procedures						
Visit Number	1	2	3	4	5	6
Time Point (Day)	-14	0	1	14 [b]	28 [b]	84 [b]
Visit Window (Day)	+/- 7	-	-	+/- 3	+/- 3	+/- 7
General Assessments	X	X	X	X	X	X
Vital Signs	X	X	X			
Islet Autoantibodies	X					
MMTT[a]	X					
HbA1c	X					
HIV, HBV, HCV serology	X					
QuantiFERON TB test	X					
EBV, CMV Serology	X					
EBV, CMV viral load	X					
Urine Pregnancy Test	X	X				
Comprehensive chemistry panel	X	X	X	X	X	X
Lipid Panel	X	X	X	X	X	X
C-reactive Protein	X	X	X	X	X	X
Direct bilirubin	X	X	X	X	X	X
Erythrocyte sedimentation rate	X	X	X	X	X	X
CBC	X	X	X	X	X	X
HLA Typing and SNP Analysis	X					
Mechanistic Assays	X	X	X	X	X	X
Pharmacokinetic Samples	X	X	X	X	X	X

[a] if not performed within 60 days of study screening visit

[b] blood draw Visits 4-6 may be conducted remotely